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Editorial

Is the "Right-to-try" a "Right of Patient" ?

Translated from the Editorial in Med Check-TIP (in Japanese) Jan 2018 : 18 (75)

Keywords:
randomized controlled trial, right-to-try, conditional early approval, real-world data, observational study

Randomized controlled trial (RCT) is a scientific procedure necessary for ultimately determining efficacy and safety of a drug. A series of deregulation that rocks it from the ground has begun in 2017. Before discussing it, let's briefly review the history of regulation of pharmaceuticals.

Since the global thalidomide disaster in early 1960's, regulatory authorities in many countries have established and applied a system in which new drugs are approved by confirming the efficacy and safety by RCTs.

Among them, the United States established the strictest regulations, which required two RCTs for the evidence of efficacy and safety. However, it has been becoming more difficult to provide them especially since 1990's when numerous new substances were discovered and invented due to advances in science and technology, and they were introduced as pharmaceuticals.

Although novel drugs such as antihypertensive agents have "action to lower blood pressure", the effect of prolonging the life span has not been proven by RCT except for a case of serious hypertension. Therefore, if RCT proved that a certain disease such as heart disease or stroke is reduced by the substance, it is accepted as a medicine. Cholesterol lowering agents and hypoglycemic agents are the other examples. Moreover, deregulation was made: such that only one RCT is required for approval of a new product. Most of the medicines currently in use are the substances approved by the deregulated requirements.

Among many agents developed and approved after 2000 by less strict regulations, some products are excluded from health insurance in Europe due to their adverse effects or inefectiveness. One such example is aliskiren, an antihypertensive agent which increased cardiovascular disease and death is still now on the market in Japan. Development of some cholesterol-lowering agents was discontinued before approval. The hypoglycemic agents approved after 2000 do not reduce cardiovascular disease. Hence in the United States, a compromise was made to approve a product which at least showed non-inferiority to a placebo as a new valuable product. However, it may be very difficult to apply this method to any medicine.

Hence a new idea, "the-right-to-try" law was promoted to allow patients to try unapproved agents that completed Phase I. It passed through the Senate in the United States in August 2017 and has been deliberated at the House as of February 2018. Even if a damage is caused by trial of an unapproved agent, the company does not take responsibility. In other words, it is a corporate responsibility avoidance measure that puts "right of patient" in front.

In Japan, the same was made possible without changing laws. The Ministry of Health, Labor and Welfare Division Chief's notification on October 20, 2017 "Conditional Early Approval System" made early approval possible with a condition of confirming validation and safety by conducting observational studies with a small number of people after approval . It is adoption of an alchemic "drug approval" method that does not require RCTs.

"Observational study" can never be a substitute of randomized controlled trial. However regulators are now allowed to approve new products by using "Observational study" or what they call the "Real-World Data". They say that "Real-World Data" need less resources with fewer patients' data and less expense while RCTs need more resources with more patients' data and more expenses. With this unbelievable logic, this procedure is being promoted.

Such an outrageous act can never be accepted.

Who benefits from the guidelines?

Translated from the Editorial in the issue 75 (Jan. 2018) as the introduction of the series: Critical appraisal of the Japanese "Practice Guidelines"

Keywords:
practice guidelines, Antibiotic Guidelines, antihypertensive, strength of endpoints, overall survival, total mortality, indirect surrogates, study design

This year, we would like to address the problems in clinical practice guidelines as our theme of the year. Guidelines are tools to guide how to perform medical practice appropriately. In the early 1990s, we were impressed by the "Antibiotic Guidelines" edited and published by Therapeutic Guidelines, a nonprofit organization in Australia. It was made in the 1970s in response to the emergence of resistant bacteria due to overuse of antibiotics in the country.

The latest version of the "Antibiotic Guidelines" at that time was translated and published in 1999 by the Japan Institute of Pharmacovigilance (now NPO Japan Institute of Pharmacovigilance) because we thought that it would serve not only for medical professionals but also for patients. We invited Mary Heming, the editorial executive of the "Therapeutic Guideline" as a guest speaker of the 2nd Pharmacovigilance Seminar in 1999. This antibiotic guideline is excellent as it clearly distinguishes the diseases or conditions in which antibiotics should be used from those in which antibiotics are not necessary based on scientific evidence. We learned from her lecture how the guidelines were born (The Informed Prescriber Oct. 1999).

It may be a desire of many people to live healthy, avoid illness, and live long. For this purpose, one would consult a medical doctor and seek medicines.

In modern science, the mechanism of the body is elucidated at the molecular level, human genetic information is precisely elucidated, many receptors and their ligands (substances acting on receptors) are discovered, and numerous potential new drugs are developed.

Since 2000, many clinical practice guidelines have been published in Japan as well. They are claimed to have been created in accordance with the Evidence-Based Medicine. In these guidelines, many references are cited, the recommendation level is determined and finally new drugs are recommended for use.

Modern medical doctors may want to believe that their therapeutic skills are much more advanced than those of 30 or 50 years ago. But is this true?

New drugs strongly act on the body: A hypotensive agent surely lowers blood pressure, a cholesterol lowering agent surely lowers cholesterol level and a hypoglycemic agent surely lowers blood sugar level. A neuraminidase inhibitor reliably inhibits neuraminidase of influenza virus. An influenza vaccine using splits of influenza virus as an antigen surely produces antibodies against them.
Various guidelines use these findings as evidence. They explain as if scientific evidence is complete and recommend new agents as useful drugs.

This makes healthcare professionals believe these agents are useful for their patients (people), and prescribe and dispense them for their patients (people).

Will diseases be cured or complications be prevented if blood pressure falls, cholesterol level goes down, and blood glucose level decreases? Will this help us become healthy? What about possible serious harm caused by medicines that may shorten the life span? As recommended by the guidelines, doctors prescribe antihypertensive agents, cholesterol lowering agents and hypoglycemic agents. Pharmacists dispose them. Patients take medicines without doubting the health professionals' medical practice of good intention.

This series will critically examine guidelines based on the evidence of proper balance of benefit and harm of products which are recommended by the guidelines. It will investigate and appraise in depth some key products to prove that they are actually ineffective or harmful as these are often neglected by various guidelines made by so-called "experts".

In this series, we evaluate new products in accordance with the instruction in the "Chapter 8 Reviewing a new drug: Is it a therapeutic advance?" in the ISDB Manual issued in 2005 (http://www.isdbweb.org/documents/uploads/manual_full_text.pdf).

In order to evaluate benefits and harm of a new product, we consider the strength of endpoints as the most important indicator to be assessed as shown in the Box 1 in the Chapter 8 of the ISDB Manual.

Strength of the evidence

From Chapter 8 of the ISDB Manual.
http://www.isdbweb.org/documents/uploads/manual_full_text.pdf

The strength of the evidence must be assessed by looking at the primary outcome measures used in the trials and at other aspects of the design of the study. The outcome measures and the design and conduct of randomised controlled trials are often inadequate, and lead to unreliable or irrelevant conclusions. Therefore careful appraisal of trial reports is needed to assess the reliability of the trial results.

When evaluating a treatment for a disease from which patients die, the most obvious and measurable outcome is whether the treatment improves survival. However, even when 'survival' is the most appropriate primary endpoint, very often in clinical trials a surrogate endpoint, such as transient symptomatic relief and/or improvement of certain laboratory tests, is used instead. The reason for this is that it allows trials to be shorter or to require inclusion of fewer patients.

Another problem is the use of combined endpoints (e.g. definite myocardial infarction (MI) and death from MI (cause-specific morbidity and mortality)). A combined endpoint may miss important effects of treatment that actually shorten overall survival and/or lead to other serious complications.5 The primary endpoint of real interest for patients is death from all causes, with all serious events, such as cancer, included in the endpoint. Box 1 shows a hierarchy of endpoints. The hierarchy is from the US National Cancer Institute and relates to evaluation of treatments for cancer, but it can be adapted to other therapeutic areas too. **Box 2** shows a hierarchy of study design.

These hierarchies do not include non-clinical evidence, which should also be considered in an evaluation – e.g. pharmacokinetic studies, dose-ranging studies, studies in healthy volunteers, toxicology (see **Box 4** and the annexe at the end of this chapter).

Box 8.1 Strength of endpoints (ranked in descending order)

A. Total mortality (or **overall survival** from a defined point in time)

Comment: This outcome is arguably the most important one to patients and is also the most easily defined and least subject to investigator bias.

B-1. Cause-specific mortality (or cause-specific mortality from a defined point in time)

Comment: Although this may be the most biologically important in a disease-specific intervention, it is a more subjective endpoint than total mortality and more subject to investigator bias in its determination. It may also miss important effects of therapy that actually shorten overall survival. For example, oestrogens in the treatment of prostate cancer.

B-2. Cause-specific morbidity alone or in combination with B-1 (*a)

Comment: It is also a more subjective endpoint than total mortality and more subject to investigator bias in its determination. It may also miss important harm induced by therapy that may actually shorten overall survival and/or quality of life.

C. Carefully assessed quality of life (i.e. assessed independently of other indicators of activity in daily life) (*b).

D. Indirect surrogates

1) Disease-free survival
2) Progression-free survival
3) Tumour response rate
4) Scales and other measures that are not clinically validated in the specific clinical condition or population (*a).

Source: Based on a hierarchy from the US National Cancer Institute web site (http://www.cancer.gov/cancertopics/pdq/levels-evidence-adult-treatment/)
*a: Added by the manual's editors, to make more applicable to other diseases and interventions.
*b: If "carefully assessed quality of life" is combined with overall survival, the combined endpoint could be classified as A-2.

Box 2. Hierarchy of study design

1a. Systematic review (with homogeneity) of randomised controlled trials or **single large-scale randomised controlled trial** (mega-trial).

1b. At least a single randomised controlled trial.

2. Systematic review of **cohort studies or non-randomised controlled trials.**

3. Systematic review of **case-control studies.**

4. Case series (includes poor quality cohort and case-control studies) (*a).

5. Expert opinion without explicit critical appraisal.

Source: Based on a hierarchy from Levels of Evidence and Grades of Recommendation by Centre for Evidence-Based Medicine, Institute of Health Sciences, Oxford
[www.cebm.net/levels_of_evidence.asp#notes]
*a: All or none case-series (i.e. when all patients died before the treatment became available, but some now survive on it; or when some patients died before treatment became available, but none now die on it, are classified as 1c).

Annual theme of 2018: Critical appraisal of the practice guidelines (1)

Guidelines for influenza treatment in Japan is misleading

Translated from Med Check-TIP (in Japanese) Jan. 2018 : 18 (75):10-12

Many doctors use practice guidelines made by various medical societies as "guidelines" for their clinical practice. However, guidelines may often be harmful for their patients. "Critical appraisal of the practice guidelines" is the annual theme of the year 2018. The first issue is about influenza management.

Summary

1. Anti-influenza agent is useless and harmful

In Japan, if you have influenza, you would see a doctor, and if a rapid test is positive, the doctor would prescribe a neuraminidase inhibitor such as Tamiflu. Experts of infectious diseases and policy makers recommend "early treatment with antiviral drugs". As a result, total prescriptions per capita of neuraminidase inhibitors in Japan is 1000 times or more than that in the UK. Sudden death due to respiratory suppression or accidental death after abnormal behavior by Tamiflu still continues to be reported.

Neuraminidase inhibitors do not inhibit the growth of viruses in human bodies, but they inhibit the hosts' endogenous neuraminidase and suppress their immunity. The reduction of symptoms after using neuraminidase inhibitors is only an apparent effect. They do not prevent severe condition and have no effect in decreasing hospitalization or death. They haves no effect in preventing influenza virus infection either. These were confirmed by the Cochrane neuraminidase inhibitor team. On the other hand, accidental deaths after abnormal behavior and sudden death due to respiratory suppression were reported after Tamiflu use. Neuraminidase inhibitors especially Tamiflu should not be used.

2. Influenza vaccine is not recommended

The guidelines recommend that people should be vaccinated annually for the prevention of influenza. However, the Japanese influenza vaccine does not prevent infection because it does not make immunity for prevention of infection at the mucosal surface of the nose and bronchus.

All observational studies that claim influenza vaccine to be effective are the results obtained by ignoring the usual health conditions (healthy vaccinee effects or healthy user bias). A large-scale survey (Maebashi survey), which was not affected by the healthy user bias, clearly showed that the influenza vaccine had no effect. This survey is most reliable. Moreover, the results of a systematic review of randomized controlled trials showed that it was ineffective for the elderly who had used the same type of vaccine as those in Japan.

In adults and children aged 16 to 65 years old, the efficacy was observed for the inactivated vaccines (not permitted in Japan). However, as many as 70 persons should be treated to prevent influenza in only one person. Although harm is rare, it may cause convulsions or Guillain-Barre syndrome, an intractable neurological disease. Influenza vaccine is not recommended.

Keywords:

influenza, guideline, Tamiflu, neuraminidase inhibitor, antiviral agent, abnormal behavior, sudden death, influenza vaccine, split vaccine, inactivated vaccine, live attenuated vaccine, Maebashi City survey

1. Neuraminidase inhibitors

Japanese guidelines recommend using them

Let's examine the 2011 proposals of The Japanese Association for Infectious Diseases [2] (JAID 2011), manual of the Japan Physicians Association (JAPHA 17/18) [3], treatment guidelines of the Japan Pediatric Society [4] (JPS 2017), comprehensive measures by Ministry of Health, Labor and Welfare [5] (MHLW 2017) and Q & A by MHLW (MHLW Q&A) [6].

Recommend drug use in all cases

The opinion described in the JAID 2011 [2], which was first presented during the outbreak of influenza in 2009, shows a fundamental idea of the society.

"As a general rule, ---- the biggest goal is to prevent severity to reduce hospitalization and death by administration of neuraminidase inhibitors." "It is most important that as much as possible, starting therapy with anti-influenza drugs at the earliest stage of the disease in all cases."

This recommendation emphasizes the importance of anti-influenza agents on the premise that "influenza gets severe", neglecting the fact that "influenza is a self-limiting infection". It claims that "neuraminidase inhibitor" can "prevent severity of influenza and recommends broad use of neuraminidase inhibitors.

As a result, "JAID 2011" [2] states that "using oseltamivir, raninamivir or zanamivir" is considered for most patients without any specific limitations.

The JAPHA 17/18 presents almost the same idea as these recommendations in JAID 2011.

The JPS 2017 also recommends antiviral use

The recommendation of JPS 2017 is slightly different. It says **"4. Most of influenza infection is self-limiting with natural cure and administration of anti-influenza drugs is not essential".**

However, before this sentence,

1. Patients such as infants, having underlying diseases or patients with strong respiratory symptoms are at high risk of severity.

2. In principle, it should be used within 48 hours after onset, but it should be considered even after more than 48 hours have passed since onset.

3. Even patients without concomitant diseases,--- anti-viral drugs can be administered by the doctor.

As 1 to 3 are written before the fourth point "4. Most of influenza infection is self-limiting with natural cure and administration of anti-influenza drugs is not essential", the true meaning of "Use of anti-viral agent is not essential' is undermined and cannot be understood by the pediatricians.

The MHLW recommends early consultation

MHLW recommends early consultation when one gets influenza as an answer to the question "What should I do with influenza?" in the "MHLW Q & A". It explains

"(1) Consult a medical doctor as soon as possible if you feel sickly"

If you notice symptoms, they recommend to see a medical doctor as soon as possible. A neuraminidase inhibitor may be prescribed as recommended by the JAID 2011, " JAPHA 17/18" or "JPD 2017" if consulted. Thus, in reality there is no restriction on the treatment of influenza in Japan.

Most antivirals in the world are used in Japan

As a result, the number of prescriptions of neuraminidase inhibitors per 1000 people in Japan is 50 times, 300 times, 1,000 times, and 1,200 times higher than in that in France and Sweden, Italy, and UK, respectively. Numerous abnormal behaviors have been reported [7].

Virus does not decrease

The general perception that neuraminidase inhibitors (NIs) such as Tamiflu inhibits the growth of viruses and lightens symptoms is a typical misunderstanding. As explained in the figure, NIs interfere with the virus leaving the cells. In the US, the label of oseltamivir does not state that Tamiflu suppresses proliferation of virus in humans. Rather, there is definite evidence that symptomatic relief is independent of virus growth suppression.

Symptom relief is due to inhibition of human endogenous neuraminidase

Respiratory syncytial (RS) virus causes pneumonia with a high mortality rate in infants. When Tamiflu was administered to mice infected with this RS viruses which had no neuraminidase, symptoms reduced, while virus load increased.

The reason is that Tamiflu inhibits the function of endogenous neuraminidase in animals and humans.

Neuraminidase is deeply involved in immune system and/or defense system. Inhibition of host's endogenous neuraminidase by NIs suppresses its action leading not to fight against viruses. Hence the symptom relief is merely the apparent effects of NIs and not the true beneficial effect for the host. As a result, unwanted disorders may occur in various organs such as renal disorders, diabetes and so on. Moreover, there is a potential danger that the symptoms worsen in the high risk persons of influenza.

Hospitalization did not reduce

A systematic review **[8]** of NIs by Cochrane team, in which I also participated and discussed, does not recommend NIs. In the revision launched in June 2017, oseltamivir (Tamiflu) was downgraded in the World Health Organization's essential medicines list (EML) from the "core" to the "complementary" list. Although it was left for use by high risk persons, Tamiflu would be deleted in the next revision **[9]**.

Among four neuraminidase inhibitors available in Japan, Tamiflu is an extremely dangerous substance, as it causes abnormal behaviors leading to accidental death and suppresses respiration leading to sudden death **[10]**. The pathogenesis of abnormal behaviors and sudden death is clear and the association is causal **[10]**. The apparent effect of the neuraminidase inhibitor on symptomatic relief and the mechanisms of the delayed reactions to Tamiflu such as reduced antibody production are described in detail in a review article **[11]**.

Although there are opinions that recommend the use **[12]** based on a systematic review by a group other than Cochrane team, a paper that criticizes them has already been published **[13]**.

Ineffective for prevention

Because neuraminidase inhibitors do not reduce proliferation of influenza virus, they have no therapeutic effect other than apparent slight symptom relief. When they were used for prophylaxis, no efficacy was demonstrated. Although a clinical trial for prophylaxis reported the efficacy, it was merely manipulation of the data from RCTs **[13]**. Because Tamiflu reduces production of antibody against influenza and viral shedding in the respiratory tract, a substantial number of patients with influenza infection showed false negative testing results by Tamiflu. These phenomena made apparent reduction of influenza patients in the Tamiflu group compared with the placebo group.

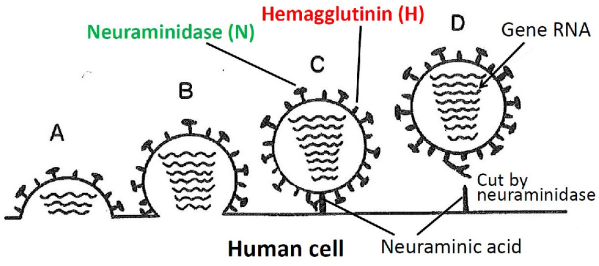

Figure 1: Budding and release of influenza virus, neuraminidase (N) and hemagglutinin (H)

The influenza virus germinates from a human respiratory cell (A, B), and finally it is connected by a saccharide chain, a neuraminic acid, to human cells (C). When this is cut by neuraminidase, the virus separates from the cell (D and E). Tamiflu inhibits neuraminidase in the virus and keeps the virus in (C) state, but it does not kill the virus. The symptoms slightly reduce because the human endogenous neuraminidase is inhibited and the immunity is weakened.

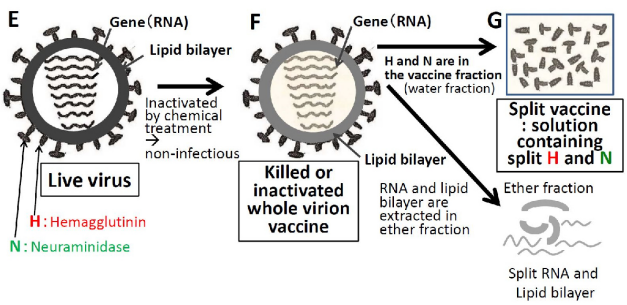

Figure 2: Live Influenza virus, inactivated whole virion vaccine and split vaccine

The influenza vaccine in Japan is a vaccine made from the above split parts H (hemaglutinine) and N (neuraminidase) (G). Vaccines that are reported effective abroad are a live attenuated vaccine or an inactivated vaccine using the whole virion (F). Split parts actually form like petal by agglutination. http://www7a.biglobe.ne.jp/SuzunokiCC/fluwa2.html

2. Influenza vaccine: ineffective and harmful

Vaccine claiming effectiveness is not available in Japan

JPS 2017 states "influenza vaccine has been reported as having efficacy preventing the onset of influenza and reducing the number of absent days at school" based on the Cochrane's systematic review **[14]**.

However, the vaccines that the systematic review reported are the "inactivated vaccine" or the "live attenuated vaccine" of spray-type on nasal mucosa, both of which have never been approved in Japan. Because strong adjuvants are added, these vaccines are more toxic than the split vaccine which is available in Japan.

Japanese split vaccine is ineffective and harmful

On the other hand, the vaccine used in Japan, as shown in the figure on the previous page, is a collection of some parts of virus and is called "split vaccine" or "subunit vaccine". Antibodies that are produced by this vaccine are those for cleaning up the parts such as N (neuraminidase) and H (hemaglutinine) dispersed in blood when the influenza virus is broken by the action of fever and immunity (see the figure on the previous page). In other words, antibodies produced by the vaccine are "antibodies for cleaning up waste". Failure to prevent invasion of influenza virus is also mentioned in "Ministry of Health, Labour and Welfare Q & A" **[6]**.

The vaccine may induce harms. Even if they are rare, it causes Guillain-Barre syndrome, neurological intractable diseases such as narcolepsy, anaphylaxis and convulsions.

No proof for reduction of "hospitalization and death"

The reference paper **[15]** that the JPS 2017 claims as the evidence of "reduction of hospitalization due to influenza" is a case-control study. Moreover, it is never reliable because one of the most important confounding factors, "healthy vaccinee effect or healthy user bias" was not adjusted.

In "HMLW Q & A" **[16]**, "evidence" claiming 34% to 55% reduction of illness and 82% reduction of deaths is cited based on the worst observational study which ignored "healthy vaccinee effect or healthy user bias".

Healthy vaccinee bias of observational studies

Please imagine the situations in which one is inoculated with a vaccine. If one has fever on the day for vaccination or one has sickness from day to day, s/he will be refrained from vaccination. Ignoring such a background, many observational studies claiming the effectiveness of influenza vaccine compare a group of persons who did not have vaccine due to diseases and a group of persons who were vaccinated due to good health.

A series of observational studies (cohort studies) by Maebashi City Medical Association of Gunma prefecture **[17, 18]** may be the only one large-scale survey comparing the frequency of influenza-like fever between groups (cities) not using the vaccine and groups (other cities) using the vaccine with similar usual health conditions. They surveyed tens of thousands of people over two years and showed no difference between the vaccinated and unvaccinated groups. It is still the most reliable observational studies for the evaluation of effectiveness of subunit vaccine in the world.

More death reported in only one RCT

Govart's trial **[19]** is the only RCT which studied the efficacy of split vaccine, the same type of vaccine as the one used in Japan, in suppressing symptoms in the elderly. According to the results, the vaccine had no efficacy for the reduction of symptoms. Rather, there were six deaths in the vaccine group compared with three in the placebo group. Randomized controlled trials of split vaccines against children and non-elderly adults only examine the rise of antibodies and none of them have examined symptomatic suppression effects.

In the Cochrane's systematic review of the RCTs for adults under the age of 65 **[20]**, only inactivated vaccines and live attenuated vaccines showed symptomatic effects. The number needed to treat to benefit was 70 showing only one person escaped influenza when 70 persons were vaccinated. There is no effect of split vaccine used in Japan.

When you have influenza

If you visit an outpatient clinic for consultation, there may be sick people or patients with high risk or elderlies in the waiting room. You may give your influenza to these people. No medical examination or medication is required for influenza, because it is a self-limiting infection with mild symptoms.

Let's think that it is a good opportunity to take enough rest and sleep with adequate nutrition and fluid. Only when you have a severe headache disturbing your sleep, low dose paracetamol may be helpful. Let's just take a rest.

For your further reference, please see my books "Preventing Encephalopathy Caused by Medicines" **[21]** and "Tamiflu is Harmful as Presumed" **[22]**.

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Annual theme during 2018: a series of critical appraisal of practice guidelines (2)

Do general health checks prolong lifespan?

Translated from Med Check-TIP (in Japanese) Mar. 2018 ; 18 (76):28-31

In this series of article, we discuss the efficacy and effectiveness of "general health checks" on all-cause mortality. First of all, in this issue, we examine randomized controlled trials (RCTs) and systematic review of them. Subsequently, we will examine the practice guidelines on hypertension, cholesterol etc., which "general health checks" find frequently as health problems or risk factors of major diseases such as ischemic heart diseases or stroke.

Summary

- A Cochrane's systematic review of randomized controled trials (RCTs) examined the general health checks on all-cause mortality for adults less than 65 years of age. After about nine years of follow-up, there were no differences on all-cause mortality between the health checks group (74 per 1000 participants) compared with the control group (75 per 1000). No difference was found by several subgroups and sensitivity analyses by various factors. There was no difference on mortality rate from heart diseases or cancer either.
- Eight RCTs (12 cohorts) which examined the general health checks on all-cause mortality in 65 years or older were found. Meta-analysis of them showed that mortality rate in the general health checks group increased by 30% compared with the control group as a whole in 65 years or older (including 75 years or older). All-cause mortality increased by 62% in the age of 75 or older (odds ratio 1.62, p = 0.0002).
- In a Finish RCT with long term follow up, after general health checks for males with 38 to 54 years of age, low risk participants were allocated into two groups; an intervention group who were treated intensively with various health problems for five years or a control group without intervention. All-cause mortality after 18 years in the intervention group increased by 54%, compared with that in the control group. There may be some problems in the measures of intervention after general health checks.
- In Japan, there is no RCT that assessed the efficacy of general health checks on all-cause mortality, but there are many surveys that support the results above. These will be discussed in detail in the next issue and thereafter.

Conclusion: General health checks do not prolong lifespan, and it seems that life expectancy shrinks on the contrary, especially in the elderly aged 75 years or older. Advices for lifestyle and method of treatment based on the current practice guidelines may be inadequate.

Keywords:
general health checks, special health examination, randomized controlled trial, death, health advice, medical intervention, intensive treatment

Introduction

"Special Health Examination" is a term used in the health examination in order to find a specific disease such as “breast cancer screening” and “lung cancer screening”. In the "general health checks", on the other hand, various examinations are performed comprehensively. It may find risk factors that may lead to future full-blown diseases. You may be intervened for dietary habits, exercise, sleep, smoking, etc. according to the results. You may be advised for taking medications in order to be healthier and to live longer.

The purpose is certainly good. However, it may really be good if the general health checks actually help you live longer. We have assessed various cancer screening examinations so far in this bulletin. As a result, we concluded that occult blood testing for colorectal cancer may be effective [1]. However, based on the best evidence available we reported that most

cancer screenings including breast cancer screening **[2,3]**, uterine cancer screening **[4]**, lung cancer screening **[5]** and prostate cancer screening **[6]** were ineffective.

In the FORUM on MedCheck TIP No. 75, in response to the questions from a reader, we preliminary wrote on the ineffectiveness of general health checks for elderly people. This time we will look at the efficacy of comprehensive general health checks for not only the elderly but also non-elderly people (less than 65 years old).

A brief history of general health checks system in Japan

In Japan, complete medical checks began in the 1950's. An automated laboratory device (autoanalyzer) was developed and introduced in the general health checks in 1970 **[7, 8]**, which enabled us to get laboratory test results within the day of examination. In 1982, Elderly Health Law was amended. Free medical expense system for the elderly was abolished and general health check system was introduced for the citizens aged 40 years or older **[9]**. In 1994, the law was revised to strengthen general health check system for people aged 40 years or older [**9**].

Comparative trials on general health checks (1)

No effect on mortality in non-elderly adults

A Cochrane systematic review that assessed the efficacy of general health checks **[14]** reported as follows:

The authors searched randomized controlled trials (RCTs) of general health checks on mortality including all-cause mortality comparing "general health check group" and control group without intervention in adults excluding the elderly. A total of 14 RCTs were found. Of these 9 RCTs reported all-cause mortality. Total participants were 155,899 who were followed for about 9 years (median) and 11,940 deaths were reported. All-cause mortality rate was 74/1000 in the health check group compared with 75/1000 in the control group. Risk ratio for all-cause mortality was 0.99 (95% CI: 0.95, 1.03). Mortality rates from cardiovascular disease (risk ratio 1.03) and cancer (1.01) were similar and showed no difference in the mortality rate between both groups.

The purpose of general health checks is to find risk factors leading to full-blown diseases early; i.e. hypertension, lipid abnormality, hyperglycemia, etc. and correct lifestyle if necessary. If intervention to life styles were not successful for improvement of risk factors, treatment by medicine may be considered. In other words, manpower and money were consumed, people consume time, move some distance to visit medical facilities to receive health checks, try to improve their lifestyles and receive medical care if necessary. As a result, you have "no effect" on prolonging lifespan. It means that everything ended in vain.

Why it has no efficacy?

Several limitations have been pointed out for this systematic review **[15]**. For example, many of the included studies have been reported before the 1970's and antihypertensive agents, cholesterol lowering agents, hypoglycemic agents are changing with the times. However, in the review, the risks ratios for all-cause mortality were reported separately before and after 1980 with no differences: risk ratios were 0.99 and 1.03, respectively.

In addition, in the Cochrane review, they conducted many subgroup and sensitivity analyses: for example, with or without lifestyle interventions, by the number of health checks, by the length of follow-up period, by geographical location, with or without examination by physician, by the degree of selection bias, performance bias and detection bias etc. In any subgroup and sensitivity analysis, the risk ratios were between 0.98 and 1.03 with no difference in all-cause mortality.

Inter99, a latest RCT published in 2014 also shows that there was no efficacy on prolonging lifespan by general health checks **[16]**. Health check group (11,629 participants) and control group (47,987 participants) were followed for about 10 years. Risk ratio for cardiovascular disease was 1.03, stroke 0.98, total death 1.00. These suggest that medical treatment using newly developed antihypertensive agents, cholesterol lowering agents, hypoglycemic agents may not be able to prolong lifespan.

There are some inadequate criticisms on the methods: participants' age was young, proportion of participants with risk factors were low, less participants had general health checks, intervention did not always lead to improvement of lifestyle and not many examinees visited medical facilities **[15]**.

Deaths increased at 18 years after general health checks and medical interventions

Let's look at the results of a randomized controlled trial that Cochrane's review did not include, but followed participants with risk factors of cardiovascular disease for 18 years **[17, 18]**.

This study was conducted in Finland. People who were between 38 and 54 years old from 1972 to 1973 were eligible. The methods were different from the Cochrane' s review in that all participants received general health

checks. People who had serious diseases such as myocardial infarction and stroke were excluded, and 1222 participants who were healthy or at least one risk factors such as hypertension, high cholesterol, smoking, obesity for ischemic heart diseases were randomely allocated to intervention group or control group.

Participants of control group (n=610) had no intervention except those with diastolic blood pressure exceeding 110 mmHg who were advised to consult a doctor. On the other hand, 612 participants in the intervention group were advised on lifestyle such as diet and smoking. If blood pressure or cholesterol level did not improve, antihypertensive agent (thiazide or β blocker) or cholesterol lowering agent (fibrate or probucol) was prescribed. The target value of blood pressure was less than 140/90 and the target value of total cholesterol was 260 mg / dL (**Note 1**). After five years of intervention, the average blood pressure decreased from 148/96 to 138/88 and the total cholesterol level decreased from about 275 mg/dL to 260 mg/dL.

In the control group, the blood pressure was decreased from 146/94 to 142/91 and the total cholesterol level remained the same level at 270 mg/dL.

After 18 years, 95 died in the intervention group while only 65 died in the control group. Odds ratio is 1.54 (95% confidence interval 1.10 to 2.16, p=0.0117). More than twice cardiovascular diseases were observed in the intervention group compared with the control group. Although advice for smoking cessation was also done, the results were disappointing.

Employers are obligated to do "health checks at workplace" which almost all employees receive in Japan. According to the results of health checks, lifestyle intervention such as diet or exercise may be given. Unless the level of indicator for health would be “improved”, it may be attributed to the lack of personal effort. However, this Finnish study clearly shows that aggressive intervention including treatment with medicines may worsen and shorten their lifespan, although interventions were given with "goodwill" after general health checks.

Note1: Target level of total cholesterol at the time the health checks was conducted.

Comparative trials on general health checks (2)

Death increased in the elderly

The Cochrane Review **[14]** is a systematic review of randomized controlled trials (RCTs) comparing health checkup group and control group without health checks and RCTs aimed at elderly people aged 65 years or older were excluded from the review. Therefore, we examined 10 trials **[19-28]** that were excluded from the review. There may be more trials other than these, but this time it is the results of the analysis of them.

Among the 10 RCTs, two **[27, 28]** were excluded from the analysis because data on all-cause mortality was not reported. As a result, 12 cohort in eight papers **[19-26]** which reported data on all-cause mortality after general health checks comparing with non-health checks after follow-up for approximately 2 years or more. These papers were published after 1990 **[20-26]** but one in 1979 **[19]**.

Data on all-cause mortality were meta-analysed and combined odds ratios and their 95% confidence interval (95%CI) were calculated by random effect model (DerSimonian-Laird) for participants of 65 years old or older and for those 75 years old or older (**Note 2**).

In total, among 12,711 participants followed for about two years or more, 996 died. In the elderly as a whole (65 years old or older), the odds of total death increased by 30% compared with those who did not receive general health checks (**Figure A+B**): combined odds ratio=1.30 (95% CI = 1.00, 1.69, P = 0.0527, I_2 = 65.2%)

There were no significant differences for the cohort of 65 years or older (excluding the cohort with the age of 75 years or older), but the results were inconsistent (I_2 = 72 %) containing results with a significant decrease and a significant increase in the mortality rate (**Figure A**).

Combined odd ratio of seven cohorts from 4 trials targeting those 75 years or older **[23-26]** showed 62% increase of all-cause mortality in health check groups than control group (**Figure B**) with no inconsistency (I_2 = 0 %).

There were 6 RCTs (7 cohorts) for 2 years of follow-up, 2 RCTs (5 cohorts) for 3 years of follow-up. There was one RCT **[20]** which followed for four years, but we used the data for the two-year follow-up period because of the least attrition bias.

Note2: "65 years or older" includes not only the participants of 65 to 74 years old but also "65 years old or older including 75 years or older”, if it cannot exclude “75 years or older".

Japanese studies also suggest harm of medical interventions

There is no RCT that assessed the efficacy of general health checks in Japan, but there are several studies that may be helpful for assessing it. For example, a cohort study called

NIPPON-DATA is one of them. From these data, you can see that the independence after 15 years is lowered by use of anti-hypertensive treatment. In a randomized controlled trial called JATOS, strict anti-hypertensive treatment may cause harm for health, including possible shortening of lifespan than mild treatment. There are some other studies showing similar results [12].

After all, general health checks, even though some abnormalities or risk factors were found, subsequent intervention by current knowledge or common sense in modern medical science may do more harm to people than good. It is especially true for the elderly aged 65 years or older. It may indicate that if people suddenly change their way of lifestyle, or take a new medicine, lifespan may be shortened rather than prolonged. In this point, practice guidelines for individual diseases may be deeply involved. We will examine the practice guidelines for individual diseases at the next issue and thereafter.

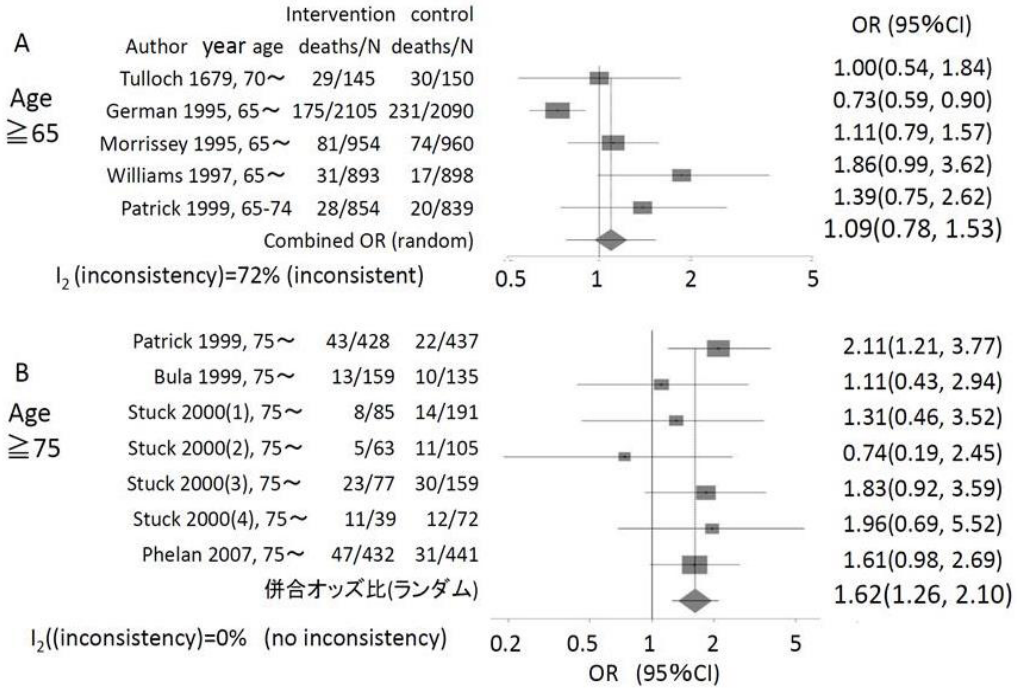
Conclusions

It is concluded that general health checks do more harm than good for the elderly 65 years or older, especially 75 years or older. It seems that general health checks may do more harm than good even for the non-elderly adults younger than 65 year old. At least it can be said that benefit does not exceed harm.

It seems that advice for lifestyle to improve risk factors of major diseases and medical intervention after general health checks rather than the checks itself may harm the health of those who received checks, even though they were done by "good will". It may rather be "unnecessary meddling".

Considering that the substantial human resources, expenses, time are required for general health checks, cost effective balance is poor. If you want to live healthy and long, it may be appropriate not to receive general health checks and not to visit a doctor unless you have or feel substantial abnormal symptoms with potential risk of your life.

Figure: Meta-analysis results of health checks on all-cause mortality



Overall elderly (65~) : combined odds ratio 1.30 (95% CI = 1.00, 1.69, P = 0.0527, I_2 = 65.2%)

65 years old or older excluding 75 years old or older: combined odds ratio 1.09 (95% CI = 0.78, 1.53, P = 0.61, I_2 = 70.2%)

75 years old or older: combined odds ratio 1.62 (95% CI = 1.25, 2.10, P = 0.0002, I_2 = 0%)

Stuck (1) and (2) are low risk groups, and (3) and (4) are high risk groups

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